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Original Research

Assessing and Contrasting Bone Regeneration Potential: Autologous Platelet-Rich Fibrin (PRF) in Extracted Sockets Following Surgical Removal of Bilateral Impacted Mandibular Third Molars

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ABSTRACT:
Background:The aim of this research was to assess and compare the ability of autologous platelet-rich fibrin (PRF) to promote bone regeneration. The PRF was applied within one of the extracted sockets following the surgical removal of impacted mandibular third molars on both sides.**Methods**:A total of 50 patients, comprising 20 females and 30 males aged between 18 and 30 years, underwent simultaneous surgical extraction of bilateral impacted mandibular third molars. In this procedure, autologous platelet-rich fibrin (PRF) was applied in one of the extracted sockets, designating the opposite side as the control. Primary closure was then performed for both sides.**Results**:The side treated with platelet-rich fibrin (PRF) exhibited superior healing and bone formation in comparison to the control side, as evidenced by notable P values: ($P = 0.06>5\%$) at 1 month, ($P = 0.00<1\%$) at 3 months, and ($P = 0.00<1\%$) at 6 months postoperatively. These results suggest a statistically significant advantage in favor of the PRF-treated side across the specified time intervals.**Conclusion**:Autologous platelet-rich fibrin (PRF) enhances and expedites the process of bone regeneration and healing within the extracted sockets.
Keywords:mandibular,Autologous,platelet-rich fibrin.

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INTRODUCTION

Wound healing is a sophisticated and dynamic biological process crucial for restoring tissue integrity after injury. This intricate mechanism involves a series of well-coordinated cellular and extracellular events that work together to repair the damaged tissue.The process commences with the inflammatory phase, triggered immediately after injury.[1] In response to tissue damage, blood vessels constrict to minimize bleeding, followed by dilation to increase blood flow to the injured area. Platelets activated at the injury site release various signaling molecules, including growth factors, initiating the healing process. Inflammatory cells, such as neutrophils and macrophages, are then recruited to clear debris and pathogens.The proliferative phase follows, involving the proliferation of new tissue to replace the damaged area. Fibroblasts produce collagen, the main structural protein in connective tissue, forming a scaffold for tissue regeneration. Angiogenesis, the formation of new blood vessels, occurs to supply nutrients and oxygen to the healing tissue. Epithelial cells at the wound edges migrate to cover the wound, forming a protective barrier.The final phase is remodeling, where the newly formed tissue undergoes maturation and organization. Excess collagen is broken down, and the tissue is reshaped to enhance its strength and functionality. This phase may take weeks to months, and the tissue gradually gains strength and flexibility.Platelets play a crucial role in the early

stages of wound healing by releasing various growth factors and cytokines. Growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), are integral to cell migration, proliferation, and differentiation. These growth factors attract cells involved in tissue repair, stimulate angiogenesis, and promote the synthesis of extracellular matrix components like collagen.[2]Autologous Platelet-Rich Fibrin (PRF), as mentioned in your initial text, is a treatment approach that utilizes the regenerative potential of platelets. PRF is rich in growth factors and fibrin, forming a natural scaffold that supports tissue healing and regeneration. When applied to the site of injury or during surgical procedures, PRF can enhance the overall healing process, including bone regeneration.In summary, wound healing is a finely orchestrated process involving multiple cellular and molecular events. Platelets, through the release of growth factors, play a central role in initiating and facilitating this intricate cascade of events, ultimately leading to the restoration of tissue integrity. Autologous PRF represents a therapeutic approach that capitalizes on the regenerative properties of platelets to enhance the healing process, particularly in the context of bone regeneration and surgical interventions.

In 1974, Ross et al. made a groundbreaking contribution by being the first to describe the growth factors derived from platelets that are entrapped within a fibrin matrix. This discovery was pivotal in understanding the role of platelets in wound healing. Platelets, small blood cell fragments, are known to release a plethora of bioactive substances, including growth factors, which play a crucial role in orchestrating the complex process of tissue repair.[3,4]Moving forward to 1990, Gibble and Ness introduced a biomaterial known as fibrin glue, alternatively referred to as fibrin sealant or fibrin gel. This innovative substance was specifically designed to serve dual purposes: to enhance hemostasis (the prevention of bleeding) and to provide adhesive properties for wound closure. The intention was not only to control bleeding but also to stimulate a mitogenic response in the bone periosteum during the normal healing process.However, as medical practices evolved, fibrin glue faced a shift in its application. Platelet concentrates emerged as a more advanced alternative, recognized for their superior healing properties. This transition was initially proposed by Whitman et al., who advocated for the use of platelet concentrates to improve the healing process.Platelet concentrates offer a concentrated source of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and others. These growth factors play essential roles in cell proliferation, tissue regeneration, and angiogenesis, all of which contribute to effective wound healing.Over the last decade, there has been extensive exploration and research into the various uses and actions of platelet concentrates. Their applications span a wide range of medical fields, including orthopedics, dentistry, and plastic surgery.[5] The ability of platelet concentrates to enhance tissue regeneration has led to their incorporation into diverse clinical scenarios, showcasing their versatility and potential impact on improving patient outcomes.In summary, the journey from the initial discovery of platelet-derived growth factors within a fibrin matrix to the contemporary use of platelet concentrates represents a significant advancement in the understanding and application of regenerative medicine. The continuous exploration of these biomaterials opens up new possibilities for improving wound healing and tissue repair across various medical disciplines.

Platelet-rich fibrin (PRF) is a specialized fibrin matrix that encapsulates platelet cytokines, growth factors, and cells, gradually releasing them over an extended period. Functioning as a resorbable membrane, PRF has demonstrated its ability to enhance bone healing. Its composition includes a tetra-molecular fibrin matrix that incorporates platelets, leukocytes, cytokines, and circulating stem cells.[6] Autologous PRF, derived from the patient's own blood, is recognized as a biomaterial that promotes physiological wound healing and facilitates new bone formation. Notably, the activation of platelets and fibrin polymerization occurs without the need for anticoagulants.While PRF has found considerable application in cardiac and vascular surgery for sealing diffuse microvascular bleeding, its versatility extends to wound management in various surgical disciplines. In general and plastic surgery, PRF is utilized to seal wound borders, facilitating cutaneous re-use. In oral and maxillofacial surgery, PRF has been incorporated into diverse procedures such as sinus lifts, implant surgeries, alveolar osteitis management, extraction socket treatments, and cyst enucleation.[7]The focus of this study is to assess the effectiveness of PRF in wound healing, specifically by comparing bone healing in sockets packed with PRF to those left to heal naturally. This evaluation is conducted following the bilateral surgical removal of impacted third molars. The study aims to contribute valuable insights into the potential benefits of incorporating PRF in oral and maxillofacial surgical procedures, shedding light on its role in optimizing the healing process and promoting bone regeneration in a clinical context.

MATERIALS AND METHODS

This clinical study was conducted on outpatients undergoing minor oral surgery for the prophylactic removal of bilateral impacted mandibular third molars. Approval for the study was obtained from the Institutional Ethical Committee to ensure ethical standards were met.

The study sample consisted of 50 patients, including both women and men aged between 18 and 30 years.

Written consent was obtained from the patients or their guardians who participated in the study. Exclusion criteria involved patients with uncontrolled diabetes mellitus, immune diseases, or other systemic conditions that could impact the study outcomes.

Each patient was categorized into one of two groups:

1. Group 1 (PRF/case side): This group underwent the surgical removal of the third molar, with subsequent placement of autologous Platelet-Rich Fibrin (PRF) in the socket, followed by primary closure.
2. Group 2 (Control side): This group underwent the surgical removal of the third molar, with primary closure of the socket. The designation of the case side or control side was randomized to ensure unbiased comparisons.

The study design, incorporating PRF as a treatment modality on one side and a standard protocol on the other, aims to evaluate and compare the outcomes of these interventions in the context of surgical removal of impacted third molars. The random assignment of case and control sides enhances the robustness of the study by minimizing potential biases. Overall, the study seeks to contribute valuable insights into the impact of PRF on the postoperative healing process in minor oral surgical procedures.

The platelet-rich fibrin (PRF) preparation adhered to a meticulous protocol established by Choukroun et al. The entire procedure unfolded under stringent sterile aseptic conditions to uphold the purity and integrity of the resulting PRF. Here is a detailed expansion of the preparation process:Approximately 20 ml of venous blood was aseptically drawn from the patient. Crucially, no anticoagulant was introduced to the collected blood, preserving its natural coagulation properties. The drawn blood was promptly transferred to sterile 15 ml test tubes, which underwent centrifugation at 3000 rpm for 10 minutes. This centrifugation process facilitated the separation of blood components based on their densities.Following centrifugation, the resultant product comprised a PRF gel, occupying a specific layer in the test tube. Careful separation was undertaken to distinguish the PRF gel from the red blood cells (RBC). An intermediate buffy coat, rich in platelets and leukocytes, was also separated as part of the PRF preparation.

The PRF gel, recognized for its concentration of platelets, leukocytes, and growth factors, was positioned between two sterile gauzes. Gentle compression of the gel between the gauzes facilitated the formation of a membrane. This membrane represented the concentrated and fibrin-rich PRF, ready for application in subsequent surgical procedures.The prepared PRF membrane was immediately employed within the extraction socket following the surgical removal of the third molars. The rich concentration of platelets and growth factors in the PRF aimed to enhance the regenerative potential and support the healing process in the extraction site.This detailed and sterile preparation process adhered to established protocols, ensuring the optimal quality of the PRF for its intended use in enhancing wound healing and bone regeneration in the oral and maxillofacial surgical context.

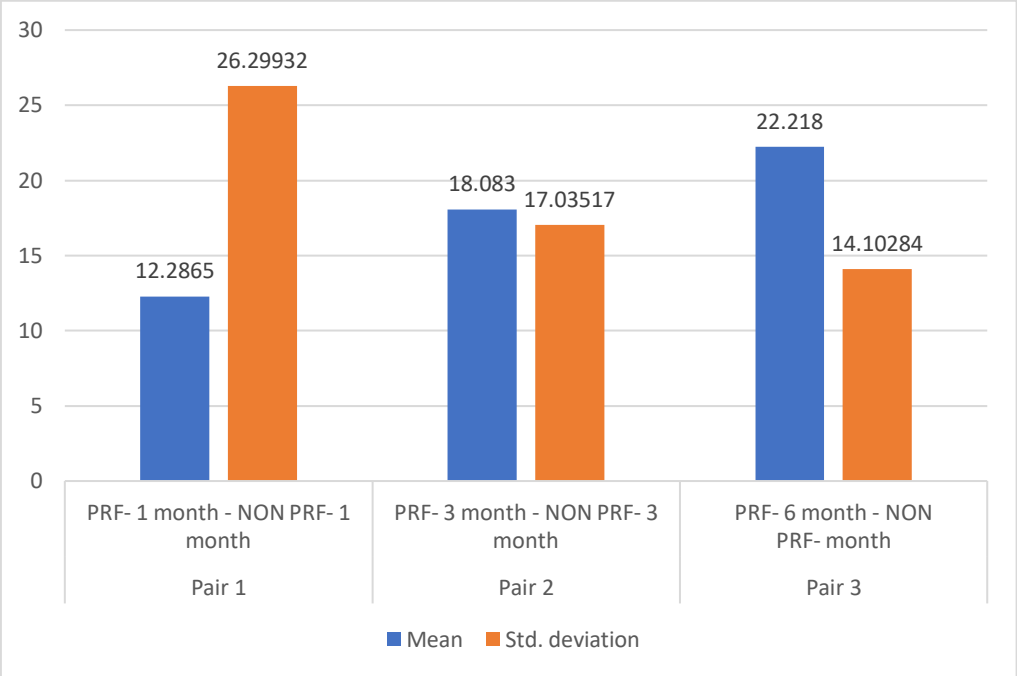
RESULTS

In this study, five patients were excluded from the analysis as they did not attend the 1st, 3rd, and 6th months of follow-up. Out of the remaining 40 patients, four experienced postoperative paresthesia on the control side, while one patient had paresthesia on the test side, which subsequently resolved after 2 to 3 weeks of follow-up. Additionally, 30 patients reported mild swelling and pain in the non-platelet-rich fibrin (PRF) region, whereas 10 patients experienced diffuse swelling and pain in the PRF region for 2 days, resolving after 3 days. No other complications, such as trismus, dry socket, or wound dehiscence, were observed.To assess statistical significance, a P-value less than 0.05 (5% and 1%) was considered. The Kolmogorov–Smirnov test was applied to continuous variables to check for normal distribution. The test results indicated that the measurements followed a normal distribution (all $P > 0.05$). This statistical approach enhances the reliability of the study findings and contributes to the comprehensive evaluation of the impact of PRF on postoperative complications and outcomes.

Table 1: Comparing PRF and non PRF using paired sample statistics

Paired Samples Test			
		Mean	**Std. deviation**
Pair 1	PRF- 1 month - NON PRF- 1 month	12.28650	26.29932
Pair 2	PRF- 3 month - NON PRF- 3 month	18.08300	17.03517
Pair 3	PRF- 6 month - NON PRF- month	22.21800	14.10284

Figure 1: Comparing PRF and non PRF using paired sample statistics



The paired "t-" test results provided valuable insights into the radiodensity changes between the PRF side and the non-PRF side during different postoperative intervals. Notably, a statistically significant difference was observed in the 1st month postoperative follow-up (P = 0.061, >5%), indicating that the PRF side exhibited a higher level of radiodensity compared to the non-PRF side during this early phase of assessment. This initial finding hinted at the potential positive influence of platelet-rich fibrin (PRF) on bone regeneration shortly after the surgical intervention.Subsequently, the paired "t-" test results revealed highly significant differences during the 3rd and 6th months postoperative reviews (P = 0.000, <1% for both). This robust statistical significance emphasized a consistent trend of increased radiodensity on the PRF side compared to the non-PRF side, further supporting the notion that the application of PRF contributes significantly to sustained bone regeneration and density over an extended period of time postoperatively.Furthermore, the results of the repeated-measures ANOVA added another layer of statistical significance, indicating a notable difference during the 1st, 3rd, and 6th months specifically on the PRF side postoperatively (P = 0.001). This comprehensive statistical analysis strengthens the evidence that the presence of PRF consistently correlates with enhanced radiodensity across multiple time points.In conclusion, these findings collectively suggest a positive and enduring impact of PRF on bone regeneration, with increased radiodensity observed on the PRF side throughout the postoperative period. This insight contributes valuable information to the understanding of the efficacy of PRF in promoting and sustaining bone healing following surgical interventions.

DISCUSSION

In response to injury, the body initiates a healing process marked by both humoral and cellular reactions within the framework of inflammation. Cytokines and biologically active growth and differentiation factors orchestrate a cascade of events to facilitate tissue recovery. Traditionally, wound healing is categorized into four distinct phases: hemostasis, inflammation, proliferation, and tissue remodeling.[9]The initial phase, hemostasis, focuses on stopping bleeding and initiating clot formation to prevent further blood loss. Platelets play a vital role by releasing factors that contribute to clotting and kickstart the healing process. Inflammation follows, serving to clear debris, pathogens, and damaged tissue from the injury site. This dynamic response involves increased blood flow, immune cell recruitment, and the regulation of activities by cytokines.The proliferation phase is characterized by the formation of new tissue, driven by fibroblasts producing collagen, the primary structural protein. Angiogenesis ensures the growth of new blood vessels to supply oxygen and nutrients, while epithelial cells migrate to cover the wound.[10,11,12]The final phase, tissue remodeling, involves reshaping the newly formed tissue to enhance its strength and functionality. Excess collagen is broken down, contributing to the gradual gain in strength and flexibility over a period extending from weeks to months.Throughout these phases, the coordinated release of cytokines, growth factors, and signaling molecules ensures a regulated wound healing process. This intricate interplay between humoral and cellular components contributes to the restoration of tissue integrity and functionality at the injury site.

In the hemostasis stage of wound healing, fibrin and its degradation products, along with macrophages and monocytes, circulate at the wound site. These cellular and molecular elements release pro-inflammatory cytokines and growth factors such as TGF-β, PDGF, fibroblast growth factor, and epidermal growth factor until the repair process is complete. The primary goal of this stage is to prevent further blood loss, and it lays the groundwork for subsequent phases of healing.Once bleeding is under control, the inflammatory phase begins, marked by the release of lipoxins and products of arachidonic acid metabolism with anti-inflammatory properties. This serves to dampen the immune response and create an environment conducive to the progression of the next stages of wound healing. The inflammatory response is finely balanced, allowing the proliferative stage to emerge once the injuring stimulus has ceased, and hemostasis has been achieved.[13,14]The proliferative stage is a complex process involving angiogenesis, the formation of granulation tissue, collagen deposition, epithelialization, and simultaneous wound retraction. Wounds typically start contracting approximately seven days after the initial injury. This phase aims to restore tissue integrity and functionality through the coordinated activities of various cell types and growth factors.The final phase of wound healing is remodeling, which leads to the development of normal epithelium and the maturation of scar tissue. This phase is essential for optimizing the strength and functionality of the healed tissue. The entire process of wound healing is highly regulated and dynamic, involving a series of interrelated events that culminate in the restoration of tissue integrity and function at the site of injury.

Platelets play a crucial role not only in the process of hemostasis but also in the complex mechanism of wound healing. These small, disc-shaped blood cell fragments contain alpha (α)-granules, which harbor approximately thirty bioactive proteins. The initiation of the activation phase triggers platelets to bind their α-granules with the platelet plasma membrane, leading to the release of a diverse array of growth factors.Among these released growth factors, key players include Platelet-Derived Growth Factor (PDGF),Transforming Growth Factor-Beta (TGF-β), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), Insulin-Like Growth Factor (IGF), and Vascular Endothelial Growth Factor (VEGF). Each growth factor serves specific functions critical to the various stages of wound healing.PDGF stimulates cell proliferation, particularly in connective tissue.[15] TGF-β plays a pivotal role in regulating cell growth, differentiation, and the production of extracellular matrix components. FGF promotes the proliferation and differentiation of cell types, including fibroblasts crucial for collagen synthesis. EGF supports the growth and differentiation of epithelial cells, essential for the formation of the outermost layer of the skin. IGF regulates cell growth, development, and metabolism, contributing to tissue repair. VEGF induces the formation of new blood vessels, ensuring an adequate blood supply to the healing tissue.The release of these growth factors from platelets is fundamental to the early phases of wound healing. It facilitates the recruitment and activation of various cell types involved in tissue repair, contributing to the proliferation of new cells, synthesis of extracellular matrix components, angiogenesis, and overall tissue regeneration. In summary, platelets serve as pivotal mediators in the initial stages of wound healing, orchestrating a coordinated and effective response to injury.

Platelet-Rich Fibrin (PRF), introduced by Choukroun et al. in France in 2001, represents a second-generation platelet concentrate designed to enhance the regenerative potential in various medical and dental applications. PRF stands out for its ability to facilitate the formation of a fibrin membrane enriched with platelets, growth factors, leukocytes, and cytokines, creating an optimal environment for tissue healing and regeneration.The preparation of PRF involves a single-stage centrifugation process, a distinctive feature of this technique. Importantly, no additives or anticoagulants are introduced during the preparation, emphasizing its autologous nature—derived from the patient's own blood.[16] This simplicity in preparation contributes to the biocompatibility and safety of PRF.The resulting fibrin membrane from PRF is characterized by its three-dimensional structure, providing a scaffold for cell migration, proliferation, and differentiation. The incorporation of platelets, leukocytes, and growth factors within this membrane is believed to play a pivotal role in accelerating the natural healing processes, particularly in oral and maxillofacial surgeries, where PRF has found extensive application.Overall, PRF represents an advancement in platelet concentrate technology, offering a practical and autologous solution for promoting tissue regeneration and wound healing without the need for external additives or anticoagulants. Its versatility and ease of preparation have contributed to its widespread adoption in various medical and dental disciplines.Platelet-Rich Fibrin (PRF) serves as a rich source of various growth factors crucial for tissue regeneration, including Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-Beta (TGF-β), and Vascular Endothelial Growth Factor (VEGF).[17,18] PDGF and TGF-β are released from platelets upon activation, often facilitated by thrombin.In the context of bone regeneration, PRF demonstrates its supportive role by releasing PDGF and TGF-β, which, when combined with Insulin-Like Growth Factor (IGF) present in plasma, contribute significantly to the intricate process of bone healing. These growth factors play multifaceted roles, promoting cell proliferation, differentiation, motility, and matrix synthesis.The interactions of PDGF, TGF-β, and IGF with specific cell surface receptors are key

events that trigger cellular responses. These growth factors act either individually or in synergy, binding to their respective receptors and initiating signaling cascades within cells. These cascades, in turn, influence various cellular processes such as the division and differentiation of cells, migration, and the synthesis of extracellular matrix components.[19,20]The collective action of these growth factors released from PRF creates a microenvironment conducive to optimal tissue healing. In the context of bone regeneration, the interplay of PDGF, TGF-β, and IGF contributes to the activation and proliferation of osteoblasts, the cells responsible for bone formation, and supports the overall regenerative process.In essence, the release of PDGF, TGF-β, VEGF, and other growth factors from PRF highlights its potential to modulate and enhance cellular responses, making it a valuable resource in regenerative medicine and various clinical applications.

CONCLUSION

Platelet-Rich Fibrin (PRF) emerges as a natural and optimized blood clot, demonstrating promising efficacy in enhancing alveolar bone regeneration within extracted sockets. The simplicity, safety, and cost-effectiveness of the PRF preparation procedure make it a viable and attractive option for patients. The application of PRF in the context of impacted mandibular third molar extraction reveals notable improvements and accelerated bone healing in the extracted socket over a six-month postoperative period when compared to the non-PRF side.The observed benefits of PRF in this specific surgical scenario underscore its potential as a valuable biological tool. The encouraging outcomes in alveolar bone regeneration prompt a call for extensive research to explore and understand the full scope of PRF's potential across various types of surgeries. The versatility of PRF in clinical applications suggests a wide range of possibilities, urging further exploration in the surgical field.As a biological resource, PRF holds promise for continued advancements in regenerative medicine. Its clinical applications are numerous, and ongoing research efforts are crucial to unlocking its full potential. The coming years are expected to witness a deeper exploration of PRF's capabilities, fostering a better understanding of its mechanisms and expanding its utilization in diverse surgical contexts. In summary, PRF stands as a compelling avenue for future research and clinical applications, with the potential to revolutionize various aspects of surgical practice.

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